REMARKS

The Examiner's withdrawal of the prior grounds of rejection under 35 U.S.C. § 112, first and second paragraphs, is noted with appreciation.

Restriction Requirement

In the January 29, 2008 response to the restriction requirement of December 31, 2007, applicant elected a composition comprising an agonist of the Toll-like 7 receptor and an agonist of a Toll-like 4 receptor, as opposed to a composition comprising an agonist of the Toll-like 8 receptor and an agonist of a Toll-like 4 receptor. Accordingly, claims 1 and 2 are amended herein to delete references to the Toll-like 8 receptor. It is believed that this amendment is sufficient to overcome the objection at page 6 of the Office Action, and withdrawal of the objection is respectfully requested.

35 U.S.C. § 103

The rejection of the pending claims as obvious over Hawkins et al. (U.S. 6,290,973), Gerster et al. (U.S. 5,389,640), and the Jannsens et al. article is respectfully traversed. For ease of reference, the following discussion as it relates to the specification of the present application will be in terms of the published application hereof, US 2007/0087009 ("the '009 publication").

The present invention as set forth in the currently amended claims relates to an immunostimulant composition comprising the combination of an agonist for a Toll-like 7 receptor (TLR 7) and an agonist for a Toll-like 4 receptor (TLR 4). The applicants have found, surprisingly, that the combination of these two agonists in a single composition provides significantly superior results (stronger Th1 orientation as measured by IL-12 production by human cells) compared to what would have been expected based on the results achieved with each agonist used independently of the other. As explained beginning at paragraph [0036] of the '009 publication, an important feature is the fact that the response observed is a potentiated response. This is surprising because previous experiments had shown that when two or more immunostimulants are present in the same composition it is "difficult to increase the response already obtained with a single immunostimulant." (id.).

The data in the present specification amply demonstrate this unexpected result. Vaccine compositions were prepared comprising no adjuvant, only TLR 4 adjuvant, only TLR 7 adjuvant, and both TLR 7 and TLR 4 adjuvant, and the four compositions were used to inoculate mice. As explained at '009 publication page 4, paragraphs [0067] – [0069], in evaluating the humoral response, it can be seen from the IgG1/IgG2a ratios reported that the vaccine composition of the present invention surprisingly exhibited a more Th1 oriented response than the response obtained when each of the control composition was used.

The cellular response also was evaluated, as explained at paragraphs [0071]-[0078] of the '009 publication. As shown in the table at paragraph [0074], the cellular response of the combination vaccine in fresh cells was substantially greater than the sum of the responses of the vaccines of the individual adjuvants. A similar result was seen in restimulated cells, as shown in the data at paragraph [0075]. The combination vaccine of the present invention also showed beneficial effects of the Th1 type response as measured in terms of cytokines: a higher level of IFN-γ which is an indicator of the Th1 orientation.

Liposome suspensions of the four test vaccines also were prepared to test the stimulation of human cells in vitro, as explained at '009 publication paragraphs [0079] – [0092]. As shown in paragraph [0094], the percentage of cells expressing markers of interest was significantly greater for the combination composition of the present invention compared to the three control compositions. As shown in paragraph [0095], the quantity of cytokines as measured in pg/ml was a *full order of magnitude greater* for the composition of the present invention compared to the control compositions. Particularly with respect to the latter measurement, the high capacity of the present invention to induce the secretion of cytokines indicating a Th1 oriented response reveals a remarkable synergy achieved by combining these two adjuvants.

In further support of the application, applicants submit herewith the Declaration of Nicolas Burdin, PhD., the first-named inventor of this application. As explained in detail therein, it was not expected that the combination of the TLR 4 agonist with either the TLR 7 agonist or the TLR 8 agonist would give improved results, because it had been found that the combination of the TLR 4 agonist with the TLR 2 agonist did not give improved results. Such a finding would have led one skilled in the art away from combinations of two TLR agonists, and

in particular away form combination of TLR 4 agonists with other agonists. *See*, Burdin Declaration at paragraph 6.

Nothing in any of the cited art suggests that such remarkable results could be achieved simply by combining two previously known adjuvants. Indeed, the fact that these two adjuvants had co-existed for many years, while nothing in the cited art suggests that anyone thought to combine them, or recognized the remarkable results that would be achieved, is further evidence of the non-obviousness of the combination. And as shown by the Burdin Declaration, those skilled in the art would have been led away from combinations of TLR agonists, and in particular combinations of TLR 4 agonists with other agonists. Such evidence of secondary considerations constitutes independent evidence of non-obviousness and can be quite instructive in the obviousness inquiry. *Sud-Chemie v. Multisorb Technologies Inc.*, 554 F.3d 1001, 89 USPQ2d 1768 (Fed. Cir. 2009), citing *Ortho-McNeill Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 86 USPQ2d 1196 (Fed. Cir. 2008).

The *Kerkhoven* case cited in the office action is inapplicable here. In that case, the invention at issue was not a composition of two different components, but a method of making the composition with two different components, in which two separate slurries of each component were used rather than a single slurry of both components. In the present case, the invention is directed to the composition itself, not a method of making it. The data throughout the specification demonstrates the unexpected results achieved by the combination.

Nothing in the cited art suggests that the combination of these two adjuvants would lead to such different and superior results in so many aspects of adjuvant performance, compared to compositions prepared with a single adjuvant. Accordingly, it is respectfully submitted that the present claims are not obvious over the cited art.

CONCLUSION

In view of the foregoing, a Notice of Allowance is respectfully requested. The applicants invite the Examiner to contact the Applicants' undersigned representative if the Examiner believes that this would expedite prosecution of this application

Respectfully submitted,

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